

## IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of

Applicant(s) : Catherine M. Verfaillie et al.  
Application No. : 10/561,826  
Filed : October 17, 2006  
Title : Neuronal Differentiation of Stem Cells  
Examiner : Chang Yu Wang  
Art Unit : 1649  
Attorney Docket : 890003-2006.1

### THIRD SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Sir:

Further to Applicants' Information Disclosure Statement filed in the U.S. Patent and Trademark Office (USPTO) on September 16, 2008 ("the Information Disclosure Statement") (copy attached), regarding the convening of a panel by the University of Minnesota ("the University"), Applicants submit this Third Supplement Information Disclosure Statement to inform the USPTO that the University has concluded its investigation of possible academic misconduct with respect to figures in the journals *Blood* and *Journal of Clinical Investigation* and in related U.S. Application No. 11/238,234 ("the '234 application"). Although the issues involved are not material to patentability, Applicants present the panel's findings in the interest of full disclosure.

More particularly, in relevant part, the panel did not find academic misconduct with respect to Western blot Figures 6 and 10 in the '234 application, though discrepancies in those figures were noted.

## **Introduction**

The '234 application discloses cells named (by the inventors) "multipotent adult progenitor cells" or "MAPCs," which, similar to embryonic stem cells, can differentiate into cell types of all three embryonic germ layers. Such cells are a novel invention. A patent application must teach how to make and use the invention. So the '234 application must teach how to make and use the MAPCs. That, even without Figures 6 and 10, it does.

## **Patentability is a Separate Issue from Academic Misconduct**

Academic misconduct may have no effect on any of the requirements of patentability. The broad scope of the definition of "academic misconduct" extends to any change in a figure, made intentionally or through gross negligence, that does not rigorously follow experimental data, regardless of the meaning and content of the disclosure as a whole, or the value of a figure as a teaching device. Under the patent law, however, one looks to the disclosure as a whole, and then only for its sufficiency in teaching the practice of the invention. Therefore, academic misconduct that does not affect such sufficiency does not detract from patentability.

As to the present case, no misconduct was found against any of the inventors with respect to either of the figures of the '234 application or the *Journal of Clinical Investigation*. The conduct of Dr. Leo Furcht, the first-named inventor in the '234 application, has not been questioned and was not involved in the investigation. Likewise, the panel concluded that there was no academic misconduct on the part of Dr. Catherine Verfaillie, the second-named inventor. Finally, while the actions of Dr. Morayma Reyes, a graduate student at the time, working under Dr. Verfaillie, were found to have involved academic misconduct with respect to four of nine figures in a paper published in the journal *Blood*, no misconduct was found against Dr. Reyes with respect to either Figures 6 and 10 in the '234 application or the *Journal of Clinical Investigation*. But, as Applicants explain below, even if misconduct had been found with

respect to Figures 6 and 10, patentability of the claims in the '234 application would not have been affected.

### **Discussion of Figures in the '234 Patent Application**

#### **Figures 6 and 10 Are Not in Provisional Applications**

Respecting the '234 application, the University investigation related only to Figures 6 and 10. The '234 application is the national phase filing of a PCT application which, in turn, is derived from two provisional filings (60/147,324 and 60/164,650). As was explained in the Information Disclosure Statement, Figures 6 and 10 in the '234 application were not a part of the two provisional filings, the content of which, even without those figures, fully describes and enables the claimed invention. This content was carried into the '234 application. Thus, the practice of the claimed invention is fully laid out in the priority provisional applications and in the '234 application whether the figures are present or not.

#### **Figures 6 and 10 in U.S. Application No. 11/238,234**

In Applicants' Information Disclosure Statement (with accompanying Forms SB/08b), Applicants have already discussed Figures 6 and 10 in the '234 application. See pages 6 and 7 of the attached Information Disclosure Statement. As to these figures, the panel's final report found that there was insufficient evidence to conclude that misconduct occurred in connection with the '234 application. However, as Applicants already have pointed out in the Information Disclosure Statement, the final report does state that the figures were flawed and not accurate data. But, even with the flaws in Figures 6 and 10, there is no negative effect on patentability for the following three reasons.

First, the flawed Western blots were duplicative and not necessary to establish functionality. Turning to the particulars of the work of the inventors, as it relates to Figures 6 and 10, MAPCs can be used to form cells with chondroblast, endothelial and osteoblast marker proteins (all are mesodermal cell types). These markers may be shown, respectively, by expression of collagen II, Tie/Tek, and bone sialoprotein. Expression of these markers may be shown by various alternative methods, such as assays of isolated

marker protein by Western blot or assay of the markers on cells that express them. Figures 6 and 10 showed marker expression by Western blots. But there were non-Western blot figures in the '234 application and both provisional applications showing expression of all three of these markers. See the attached chart for the two provisional applications and the '234 application showing expression of collagen II, bone sialoprotein, and Tie/Tek, as determined by direct assay of the cells expressing these proteins. Thus, the Western blots of Figures 6 and 10 are not even necessary to show that these marker proteins are expressed.

Second, the statements in the '234 application about the results in the Western blots of Figures 6 and 10 are accurate. All statements about expression of the three markers are factually correct and reflect the inventors' true data in that they are based on accurate Western blots that were not filed in the '234 application. As Applicants pointed out in the Information Disclosure Statement, the actual Western blot experiments showing that the cells could be differentiated to progeny cells expressing collagen II, bone sialoprotein, and Tie/Tek had been done prior to filing the '234 application. Therefore, the technically correct Western blots were, in fact, available. But, whether or not the technically correct blots were used in the figures, the person or ordinary skill would have been properly guided by the statements and the results described in the provisional applications and the '234 application.

Third, none of the claims are drawn to the markers at issue. Therefore, even if differentiation into chondroblast, endothelial, and osteoblast cells had never been shown, the patentability and scope of the claims would not be affected. Claims are directed to MAPC that can form cells with mesodermal phenotypes. The specification supports these claims by disclosing mesodermal cell types in addition to chondroblast, endothelial, and osteoblast. A person of ordinary skill would have understood from this alone that MAPCs can differentiate into mesodermal cell types. Thus, the errors do not affect the adequacy of the written description.

Respecting enablement, the errors would not have interfered with the ability of the person of ordinary skill in the art to make and use MAPCs. The specification states that MAPCs form the cell types at issue. While the blots actually showed a different protein, the errors did not detract from the ability of the person of ordinary skill in the art to make and use the MAPCs as is correctly described in the '234 application. Thus, the errors do not affect enablement.

#### **Investigation with Respect to Journal Articles**

A statement by the University, provided to the public, is attached to this Third Supplemental Information Disclosure Statement. While the two journal articles do not relate to the '234 application, for the sake of completion the same are discussed.

*Journal of Clinical Investigation* The University has accepted the panel's conclusions that, based on federal regulations and University policy, no falsification was involved in data published in the *Journal of Clinical Investigation*.

*Blood* The University also accepted the findings that academic misconduct was involved respecting some of the data published in the journal *Blood* in 2001. Dr. Catherine Verfaillie and Morayma Reyes, current and former University employees, respectively, were the subjects of the investigation. They are both co-inventors together with Dr. Leo Furcht in the '234 application. Allegations against Dr. Verfaillie were unsubstantiated. The panel concluded that, in the case of Dr. Morayma Reyes, academic misconduct was involved. This is explained in detail below.

Although, originally, only two figures were erroneous, all seven figures in the *Blood* paper were examined with respect to source blots and final figures. These seven figures are Western blots of bone sialoprotein, osteonectin, collagen II, PPAR gamma, FT myosin, vWF, and Tek.

With respect to the osteonectin, collagen II, FT myosin, and Tek blot figures in the *Blood* paper, the panel concluded that aspects of the source figures (original radiographic blots) were altered in such a way that

the manipulation misrepresented experimental data and sufficiently altered the original research record to constitute falsification under federal regulations and University policy. In finding misconduct, the panel was required to find whether the falsifications were the result of honest error or deliberate. The panel reached conclusions of misconduct by considering the totality of the circumstances. The showing of manipulations (discussed below) undermined the panel's ability to conclude that other discrepancies were the result of honest error.

#### **Specific Details About Blots Underlying Figures in *Blood***

Osteonectin The osteonectin blot was altered to eliminate a light band in the MPC lane. The panel concluded that this manipulation significantly departed from accepted practices in the research community, was done knowingly rather than through honest error, and constituted academic misconduct by Dr. Reyes.

Collagen II The beta actin blot in reverse orientation was used. A lane labeled "MPC" was added to the collagen II blot. The panel concluded that these actions significantly departed from accepted standards of the research community, were done knowingly rather than through honest error, and constituted misconduct by Dr. Reyes.

FT Myosin The FT myosin source blot was manipulated to cover an object in the MPC lane. The panel concluded that this action significantly departed from accepted standards of the research community, was done knowingly rather than through honest error, and constituted misconduct by Dr. Reyes.

vWF The panel found no misconduct in connection with the vWF figure because it cannot be substantiated. All exposures of the source blot for the published figure were missing and there was no basis to determine the blot was manipulated and no evidence to suggest that it was destroyed deliberately.

Tek The Tek blot was altered to cover image density in the MPC lane. The panel concluded that this action significantly departed from accepted standards of the research community, was done knowingly rather than through honest error, and constituted misconduct by Dr. Reyes.

### **Conclusion**

In conclusion, the specification fully supports and enables making and using MAPCs. Discrepancies identified by the University panel are limited to duplicative subject matter and, thus, do not affect the adequacy of the disclosure. While irrelevant to patentability, no academic misconduct was found against inventors Dr. Leo Furcht and Dr. Catherine Verfaillie. While academic misconduct was found respecting Morayma Reyes, it did not relate to the '234 application. It is thus clear that the claims are fully supported and enabled.

Non-Western Blot Immunoassay

<u>Marker</u>	<u>60/147,324</u> (Provisional)	<u>60/164,650</u> (Provisional)	<u>11/238,234</u>
Bone sialoprotein	Figures 5, 6	Figures 5, 6	Figure 6
Collagen II	Figure 7	Figure 7	Figure 6
Tie/Tek	Figures 16, 17	Figures 16, 17	--



To the knowledge of the person signing this Statement, after making reasonable inquiry, no item of information contained in the Third Supplemental Information Disclosure Statement was known to any individual designated at 37 C.F.R. 156(c) more than three months prior to the filing of the Information Disclosure Statement.

Applicants submit herewith two (2) Non-Patent Literature Documents.

Applicants do not believe that any fees are due with this submission. In the event that fees are incurred, the Director is hereby authorized to charge any deficiency to our Deposit Account No. 20-0809.

Respectfully submitted,



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